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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/796,280	03/10/2004	Michele Cargill	CL1510ORD	9662

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
10/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/796,280	CARGILL ET AL.	
	Examiner	Art Unit	
	JEANINE A. GOLDBERG	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2008*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6 and 25-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6 and 25-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 25, 2008 has been entered.

2. This action is in response to the papers filed July 25, 2008. Currently, claims 1, 6, 25-45 are pending.

3. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

4. Any objections and rejections not reiterated below are hereby withdrawn.

Priority

5. This application claims priority to provisional applications 60/453,050 filed March 10, 2003 and 60/466437, filed April 30, 2003.

Drawings

6. The drawings are acceptable.

New Matter

7. Claims 26, 31, 36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, reference to "the LPA gene" is included. The specification does not describe or discuss "LPA gene". The specification does not provide any description of the marker in the LPA gene. The concept of "LPA gene" does not appear to be part of the originally filed invention. Therefore, "the LPA gene" constitutes new matter. Applicant is required to cancel the new matter in the reply to this Office Action.

8. Claims 38-45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, reference to "providing a report of the identity of the SNP", "report is in paper form or computer readable medium form" are included. The amendment does not provide any support in the specification for the new language but states no new matter has been entered. A review of the specification does not describe or discuss "providing a report of the identity of the SNP", "report is in paper form or computer readable medium form". Instead the specification describes a variety of structural formats for the input and output means can be used to input and output the information in the computer-based systems of the present invention. An exemplary format for an output means is a display that depicts the presence or absence of specified nucleotides (alleles) at particular SNP positions of interest. Such presentation can provide a rapid, binary scoring system for many SNPs simultaneously in para 414. This description does not support "providing a report of the identity of the SNP", "report is in paper form or computer readable medium form". The specification makes no mention of creating a report and any type of form for the report. The concept of "providing a report of the identity of the SNP", "report is in paper form or computer readable medium form" does not appear to be part of the originally filed invention. Therefore, "providing a report of the identity of the SNP", "report is in paper form or computer readable medium form" constitutes new matter. Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 6, 25-45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1, 6, 25-45 are drawn to a method for identifying a human who has an altered risk for developing coronary stenosis by detecting a SNP in said human's nucleic acids *"as represented"* by position 101 in SEQ ID NO: 19350 in said humans nucleic acids wherein the presence of an A at position 101 (i.e. an A/A or A/G genotype) indicates a decreased risk of developing coronary stenosis and the presence of a G at

position 101 (i.e. an G/G or a G/A genotype) indicates an increased risk of developing coronary stenosis.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches polymorphisms in Apolipoproteins which are not associated with severe aortic valve stenosis. APOA, AK38, plasminogen gene are all synonyms of LPA which the instant polymorphisms lies within. Avakian et al. (Clinical Genetics, Vol. 60, pages 381-384, 2001) teaches a G/A polymorphism APO A1 which is not significantly associated with AS (see Table 3). Thus, it is clear that not all polymorphisms in the gene APO A1 is associated with each stenosis.

Further, the art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

The art teaches that presence of SNPs in the same gene does not indicate that each of the genes is associated with the same diseases. Meyer et al. (PG Pub 2003/0092019), for example, teaches that SNPs in the CADPKL gene are not each associated with neuropsychiatric disorders such as schizophrenia. Specifically Meyer teaches that cadpkl5 and cadpkl6 are not associated with the disease, however cadpkl7 has a p-value of less than 0.05, and therefore an association exists. Each of these polymorphisms are SNPs within the CADPKL gene, however, it is apparent that they are not all associated in the same manner with disease. Thus, Meyer exemplifies that the association of a single SNP in a gene does not indicate that all SNPs within the gene are associated with the disease.

Guidance in the Specification.

The specification teaches hCV2590271, SEQ ID NO: 19,350 was analyzed in S0012 and V0002 samples. As seen in Table 7, page 5, the hCV25930271 is not significantly associated with coronary stenosis in the second population (p-value 0.41193). It is thus unpredictable whether the SNP is predictably associated with stenosis given the unpredictable association in two different stenosis populations. The specification teaches there is an association between the SNP and coronary stenosis in population 1. However, it is unpredictable given the varying statistical data provided in

the specification whether the skilled artisan could make and use the instant invention without further unpredictable and undue experimentation.

Neither the specification nor the responses specifically address the concept of heterozygote individuals and homozygosity. The Table 7 merely states the frequencies of T allele. The specification appears to teach that the presence of a T allele is significantly associated in population S0012, but not in population V0002. The detection of a T or complementary A allele would thus encompass both heterozygotes and homozygotes with either an AA or AG. Thus, the mere detection of a G or complementary C allele at position 101 would not necessarily indicate an increased risk of coronary stenosis since the specification appears to include these individuals in the analysis of the A allele. If a person is a heterozygote with a GA genotype, it is unclear how the person may be at both an increased and a decreased risk for coronary stenosis.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied prior to being able to practice the claimed invention as broadly as written. This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Because the breadth of the claims encompasses a heterozygous genotype (i.e. A/G) as indicative of both increased risk (claims 1, 28) and decreased risk (claims 1, 33)

of developing coronary stenosis, it is relevant to point out that the data presented in Table 7 does not clearly indicate a significant association with the asserted risk allele and stenosis risk. Furthermore, neither the S0012 or V0002 data indicates any additive effect of risk alleles on the risk of coronary stenosis.

The claims are broadly drawn to the detection of any polymorphic content that is 'represented by position 101 of SEQ ID NO: 19350', where the specification provides no limitations as to what is required for any polymorphic position in the human genome to be 'represented by position 101 of SEQ ID NO: 19350', it is relevant to point out that in general the art is highly unpredictable with regard to the functionality of a given genomic polymorphism. In the instant case the language of the claims encompasses, in addition to the particular nucleotide content disclosed in the instant specification, other sequences such as any gene homologs or polymorphisms that are in linkage disequilibrium with the disclosed sequence that can be considered to be 'represented by' the disclosed sequence. After a polymorphism is identified, it is unpredictable whether any such polymorphism would be associated with any phenotypic trait in every population.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the art teaches the unpredictability of associating polymorphisms with disease, it is unpredictable any polymorphisms is associated with altered risk any stenosis in any individual. Further, the prior art and the specification provides insufficient guidance to

overcome the art recognized difficulties of association. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection.

The declaration of May M. Luke filed May 29, 2008 under C.F.R. 1.132 has been thoroughly considered and has been deemed persuasive to the extend it applies to the association between stenosis and the SNP at position 101 of SEQ ID NO: 19350.

The response submits that heterozygotes have an increased risk for coronary stenosis as compared to individuals wit the AA. The specification fails to provide any guidance as to heterozygotes. The specification, at the time the invention was made fails to provide any enablement for heterozygotes being either at increased or decreased risk of coronary stenosis. Table 7 appears to be directed to detection of the T or complementary A allele. Thus, the heterozygotes would appear to have been analyzed with the TT allele. There is no guidance that the heterozygotes should be analyzed with the GG alleles.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims1, 6, 25-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1, 6, 25-45 are unclear over recitation of the phrase 'as represented by', as recited in each of claims 1, 28, 33, in reference to the relationship between 'SEQ ID NO: 19350' and 'the LPA gene". The specification does not define what elements (eg. percent identity of percent similarity) are required for any gene to be 'represented by' any particular SEQ ID NO. Thus it is unclear if Applicants are in fact requiring some particular sequence context for the detected polymorphism at position 101 in SEQ ID NO: 19350.

Conclusion

11. No claims allowable.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For

more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

/Jeanine A Goldberg/
Primary Examiner, Art Unit 1634
October 14, 2008